A4 concluded

52. (Amended) An oligonucleotide according to claim 25, wherein the modified internal phosphate group or groups is a phosphorothioate.

A5

54. (Amended) An oligonucleotide according to claim 27, wherein the modified internal phosphate group or groups is a phosphorothioate.

A6

61. (Amended) A composition for inhibiting the replication of HTLV-III or gene expression of HTLV-III in a cell comprising an oligonucleotide according to any one of [claims 17-27] claims 17-19, 21-25 and 27 and [a pharmaceutically] an acceptable carrier.

A7

64. A composition for inhibiting the replication of HTLV-III or gene expression of HTLV-III in a cell comprising an oligonucleotide according to any one of [claims 44-58] claims 44-46, 48-52, 54-56, and 58 and [a therapeutically] an acceptable carrier.

REMARKS

The Applicants gratefully acknowledge the courteous and professional Examiner's Interview conducted by Examiner L.E. Crane and Supervisory Patent Examiner Douglas Robinson.

Solely in an effort to expedite and advance prosecution of this application, the Applicants hereinabove request cancellation of claims 1-16 , 20, 26, 28-43, 47, 53, 57, 59, 60, 62, 63 and 65-70 without prejudice. The Applicants maintain that these claims are patentable and reserve all rights to pursue them in future prosecution.

The Applicants have amended claim 17 to more clearly define the claimed subject matter. In particular, the Applicants amended claim 17 to recite that the claimed

oligonucleotides are from 14 to 50 nucleotides in length. Support for this amendment can be found in the specification on page 12, lines 1-10, for example, wherein it states, "oligonucleotides used to inhibit HTLV-III will be 8-50 nucleotides in length" and further specifies that the oligonucleotides exemplified in the specification range from 14 to 26 nucleotides in length. Thus, the Applicants have fairly disclosed oligonucleotides having lengths of 8, 9, 10, 11, 12, 13, 14 . . . 50 nucleotides. Accordingly, this amendment introduces no new matter.

The Applicants have also amended claim 17 by more clearly defining what is meant by the term "modified." Support for this amendment can be found on page 12, lines 19-26, for example. Thus, this amendment, too, introduces no new subject matter.

Rejection of claims 1-27 and 59-61 under 35 U.S.C. § 103

Claims 1-27 and 59-61 were rejected as obvious over Ts'o (U.S. Patent No. 4,469,863). For the following reasons, the Applicants respectfully traverse this rejection.[1]

In order to render a claimed invention obvious, the prior art must provide both a suggestion to make the claimed invention and imbue the ordinary artisan with a reasonable expectation of making and using it. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Furthermore, the prior art must suggest the *particular* form of the invention and how to make it; general guidance is insufficient. *In re Deuel*, 34 U.S.P.Q.2d 1210, 1215 (Fed. Cir. 1995) ("A general incentive does not make obvious a particular result, nor does the existence of

[1]The Applicants note that claims 1-16, 20, 26, 59, and 60 have been canceled herein and, therefore, this § 103 rejection is moot with respect to these claims.

techniques by which those efforts can be carried out."); and *In re Obukowicz*, 27 U.S.P.Q.2d, 1063, 1065 (Bd. Pat. App. Int. 1992) (Prior art "that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it . . . does not make the invention obvious."). As is described below, Ts'o is insufficient to render the present claims obvious.

Ts'o discloses oligonucleotide alkyl and aryl phosphonates. In particular, Ts'o discloses the synthesis of, *inter alia*, a methylphosphonate octamer (*see* Table VI) and states that cellular uptake studies were performed with, *inter alia*, a thymidylate nonamer (*see* col. 25, lns. 55-57). As noted by Ts'o at col. 26, lns. 42-44, "The present studies demonstrate the ability to join blocks of protected methylphosphonates to give oligomers with chain lengths up to nine nucleotidyl units." In addition, Ts'o discloses the results of experiments of the effect of various oligodeoxyribonucleoside methylphosphonate di-, tri-, and tetramers on cell-free aminoacylation to tRNA and protein synthesis. Ts'o fails, however, to provide any suggestion of an oligonucleotide having a length of 14-50 nucleotides having at least one modified internucleoside phosphate, which oligonucleotide is complementary to an HTLV-III nucleic acid. That is, Ts'o's fails to suggest the particular compounds and compositions presently claimed.

Furthermore, Ts'o fails to provide sufficient data to imbue the ordinary artisan with a reasonable expectation of successfully making and using such oligonucleotides. There is insufficient data to determine whether modified oligonucleotides of the length recited in the present claims and targeted against HTLV-III nucleic acids would be taken-up by cells in sufficient amounts to inhibit nucleic acid expression of HTLV-III. There is insufficient data

to determine whether such oligonucleotides would in fact inhibit HTLV-III nucleic acid expression. Indeed, the longest oligodeoxynucleotide methylphosphonates Ts'o tested for inhibition of protein synthesis was a tetramer, and that was in a **cell-free** system at **22°C** at oligomer concentrations of **175-200 µM** (*see* Table XI). By contrast, the oligonucleotides of the present invention have been shown to inhibit protein synthesis in **cell cultures** at **37°C** at oligomer concentrations as low as about **1 µM**. The ordinary artisan could not anticipate such results based on the teachings of Ts'o.

In view of the foregoing, the presently claimed oligonucleotides and compositions cannot be obvious over Ts'o. Accordingly, the Applicants respectfully request reconsideration and withdrawal of this § 103 rejection.

Rejection of claims 1-70 under 35 U.S.C. § 112, first paragraph

Claims 1-70 were rejected for lacking an enabling disclosure.[2] The Examiner asserted that the specification fails to enable the ordinary artisan to use the presently claimed oligonucleotides for either *in vitro* or *in vivo* purposes, and, therefore, he has asserted that the claims are not enabled. For all of the following reasons, the Applicants respectfully disagree.[3]

[2]While only claims 59-70 (the composition and method of use claims) were expressly rejected as not enabled (*see* Examiner's Action, paper no. 5, at top of page 7), in the last paragraph of page 6 the Examiner also stated that the compound claims were also not enabled under § 112, first paragraph. Accordingly, the Applicants assume the rejection is of all claims 1-70.

[3]The Applicants once again note that claims 1-16 , 20, 26, 28-43, 47, 53, 57, 59, 60, 62, 63 and 65-70 have been canceled, rendering the present § 112, first paragraph, rejection moot with respect to them.

The Federal Circuit has held that only a single utility is both necessary and sufficient to support the patentability of a claimed invention. *Stifhung v. Renishaw Plc,* 945 F.2d 1173, 1180 (Fed. Cir. 1991) ("When a properly claimed invention meets at least one stated objective, utility under § 101 is clearly shown."); *see also In re Gottlieb*, 328 F.2d 1016, 1019 (C.C.P.A. 1964) ("Having found that the antibiotic is useful for *some* purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful."); *In re Malachowski*, 530 F.2d 1402, 1405 (C.C.P.A. 1976) ("Having found that the claimed composition has utility as contemplated in the specification, § 101 is satisfied and it becomes unnecessary to decide whether it is in fact useful for the other purposes indicated in the specification as possibilities."). Since only a single utility need be demonstrated, it necessarily follows that only a single utility need be enabled.[4]

The present specification clearly enables the *in vitro* utility of the presently claimed compounds and compositions. As described starting on page 18, line 16, of the present specification, the oligonucleotides of the present invention can be used for *in vitro* assays to determine whether HTLV-III is present or absent in a sample fluid. Examples 3 and 4 of the present specification describe actual experiments in which oligonucleotides according to the present claims effectively inhibited HTLV-III nucleic acid expression in cell culture, which is the basis of the assay described. Therefore, it would require no undue experimentation for those of ordinary skill in the art to follow the express teachings of the specification to use the claimed oligonucleotides for their *in vitro* utility.

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[4]Although the Applicants maintain that the specification enables *in vivo* use as well, they find it unnecessary at this time to argue that point in view of the plain enablement of the *in vitro* utility, as demonstrated below.

In view of the foregoing arguments, the Applicants respectfully request reconsideration and withdrawal of this § 112, first paragraph, rejection.

Rejection of claims 1-70 under 35 U.S.C. § 112, second paragraph

Claims 1-70 were rejected as indefinite. The use of the phrase "consisting essentially of" was objected to in claims 1, 9, and 17 as being improper for compound, rather than composition, claims. The Applicants have deleted this phrase and inserted the word "having" therefor.

The Examiner objected to the phrase "the region of the HTLV-III encoding a frameshift" in claim 25. While the Applicants maintain that the term would be understandable to those skilled in the art, in an effort to expedite prosecution claim 25 has been amended by deleting the objected to phrase.

The Examiner objected to the phrase "the modified internal phosphate group is a phosphorothioate group" in claims 28-54 because, it was asserted, the usage would appear to exclude multiple phosphorothioate modifications. As the Examiner surmised, this was not the Applicants intention, and they have accordingly amended remaining claims 44-46, 48-52, 54 to reflect the intent (supported in the specification) that the claimed oligonucleotides are not limited to a single phosphorothioate modification.

The Examiner asserted that claims 59-64 were internally inconsistent in the use of the terms "pharmaceutically" and "therapeutically" as modifiers of the noun "carriers." The Applicants have amended remaining claims 61-64 by deleting the terms "pharmaceutically" and "therapeutically," thereby rendering this objection moot.

In view of the foregoing amendments and remarks, the Applicants respectfully request reconsideration and withdrawal of this § 112, second paragraph, rejection.

Rejection of claims 1-70 for obviousness-type double patenting

Claims 1-70 were rejected for obviousness-type double patenting over U.S. Patent No. 4,806,463 and allowed application Serial No. 07/882,073. In response, the Applicants will file appropriate terminal disclaimers when the claims are otherwise deemed allowable.

In view of the foregoing amendments and remarks, the Applicants respectfully request reconsideration and withdrawal of the pending §§ 103 and 112 rejections of claims 17-19, 21-25, 27, 44-46, 48-52, 54-56, 58, 61, and 64.

If there are any questions concerning this Response or this application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

Date: December 22, 1995

By: _____

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